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feature in their pharmaceutical and medical work. One of the most up-to-date gardens I have had the pleasure of examining is located at the University of Minnesota, where there is not only a garden of about three acres and a covered space of about three-fourths of an acre, but also a large greenhouse connected with the college of pharmacy, which the medical profession, as well as the drug trade, has seen fit to not only acknowledge of great value, but from a commercial as well as a scientific point of view it has been exceedingly beneficial in every respect.

I regret to say that the appeals of the dean of the school of pharmacy of the University of Kansas for a botanical garden for medicinal plants and for a properly constructed greenhouse thus far have not been permitted to come before the legislature. I feel that this is a very great mistake, but until we can convince the public that such a demand as I felt myself to be worthy of bringing to the notice of the legislature, we shall still remain as we are now, very backward in this most worthy enterprise.

UNIVERSITY OF KANSAS, LAWRENCE.

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# ISOLATION OF TOXIC PRINCIPLES OF COFFEE, AND THE DETERMINATION OF THEIR TOXICITY.

L. E. SAYRE.

IN 1907 the writer published, in Merck's Report, an article on the toxic principle of coffee, and since that time, in the Transactions of this Society, he has had articles on the same subject, so that he has deemed it fit to present another article, bringing forth more recent work on the subject.

The cause of toxicity of coffee has long been a mooted question. At first the toxicity was believed to be due to caffeine, but it was quickly recognized that the symptoms that sometimes follow the use of coffee are not the same as those resulting from an equivalent amount of caffeine, as is seen from the following examples:

*First.* Persons who are affected with headache, insomnia, nervousness, etc., by the use of coffee are often similarly affected by the mere breathing of the vapors given off during the boiling of coffee.

*Second.* Persons not affected by coffee drinking, and even accustomed to the vapor given off during the roasting of coffee, have the ordinary symptoms due to the use of coffee through breathing the vapors driven off during the well-known vacuum treatment of coffee, or the roasting of this product.

*Third.* Persons unable to drink coffee without suffering the above symptoms are able to drink vacuum-treated coffee without suffering in the least.

M. Burmann also points out that, of the caffeine-containing plants, tea, kola nuts and coffee, the drinks prepared from those richest in caffeine produce the least disagreeable effects, and that coffee, which requires for preparation a process of roasting, produces the most disagreeable effects.

These and other similar facts prove almost conclusively that some other principle than caffeine is responsible for the toxic effects of coffee. So insistent has been the demands for an explanation of the cause of this toxicity that efforts have been made to assign it to the small amount of potassium salts which coffee contains, or to a new alkaloid in the green bean, which has not been isolated. But lately several investigations have been carried on in which an active volatile constituent has been separated from the roasted product. For this reason the fact is fairly well established that the toxic principle, as well as the aromatic principle, is due to the products formed in roasting. In the ordinary process of roasting, the green beans, continually agitated, are heated to a temperature varying around 210° C.

From a consideration of an analysis of green coffee by Konig, the effects of a temperature over 200° C. is quite evident.

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| Water | 10.73 |
| Nitrogenous substances | 12.64 |
| Caffeine | 1.07 |
| Sugar | 8.62 |
| Other nitrogen-free extractive substances | 19.30 |
| Dextrine | .86 |
| Tannic acid | 9.02 |
| Crude fiber | 24.01 |
| Fat | 11.80 |
| Ash | 3.02 |

Of these substances only moisture and caffeine are volatile, but since many nonvolatile vegetable substances decompose below 200° C., the startling figures obtained concerning the effects of roasting can be readily believed. It has been found that over nine percent of organic material is lost while developing a light-brown color. The lost caffeine is but a fraction of one percent, and as the remaining organic substances can only escape by means of decomposition products, this result shows at least nine percent decomposition. How much takes place without escape of the resulting products cannot be stated.

The results of this decomposition and destructive distillation of the constituents of green coffee are, perhaps, as follows:

Carbohydrates yield furfuraldehyde.
Fats yield acrolein.
Tannins yield catechol, pyrogallol.
Caffetannic acid contains catechol.
Proteins contain ammonia, amines and pyrroles.

These products of roasting may also interreact to produce many compounds, such as—

Acrolein + ammonia = methyl pyridine.
Methyl pyridine + furfuraldehyde = furfural vinyl pyridine.

This latter compound will produce, on reduction, the alkaloid coniine, which is highly toxic and may be found in the coffee.

As a result of the above facts many investigators have tried to separate these products of roasting, mainly by steam distillation, and to give them careful examination as to the toxicity of the compounds found.

Bernheimer found hydroquinone, methyl amine, pyrrole and acetone. Erdmann has found furfuryl alcohol, mixed phenols, valeric acid and furfuraldehyde. Catechol has since been identified as being present. Hydrocarbons have been found that point to the presence of pyridine.

Mr. Paul D. Potter, chief chemist for Sprague, Warner & Co., has given us much information upon this subject, and among other things has given the following authoritative information on the toxicity of the various substances found in the volatile principle:

> "Of the phenols, catechol is more toxic than carbolic acid, and pyrogallol is more toxic than catechol. The harmful influence of the pyridine bases increases with the molecular weight. According to Kendrick and Dewar, they constitute the toxic part of tobacco smoke, and Williams and

Walters have found that B lutidine affects the heart profoundly. Furfuraldehyde is considered to be the deleterious agent in raw spirits, and produces a persistent headache in doses of 0.096 grams. Furfuryl alcohol in doses of 0.5 to 0.6 grams per kilo of body weight will kill a rabbit. The symptoms are lowering of the body temperature, diarrhea and respiratory paralysis. If the nitrites are present, we have in them compounds which, according to Reid Hunt, approach the cyanides in toxicity. The reaction products which may be formed from substituted pyridines (or pyrroles) and furfuraldehyde are of exceeding interest in this connection, for their structural formulæ show them to be closely allied to the highly poisonous alkaloids such as nicotine and coniine.

"In considering the toxic influence of these compounds the possible presence of bodies built up by union of the primary decomposition products should not be regarded as far fetched. It is indeed difficult to account for the presence of pyridine in any other way. Further, although furfuraldehyde is the natural decomposition product of carbohydrates, furfuryl alcohol is the principal furane body in coffee oil. Active reducing conditions therefore exist within the coffee bean during roasting.

"It would also be erroneous to conclude that, since the flavor of coffee is due to roasting, all of the decomposition products are necessary to a good product. The flavor is, of course, due to one or more of them, but since it can be developed by longer roasting at a considerably lower temperature than is customary in commercial work, it does not follow that all of the decomposition products are desirable. In fact, Erdmann claims to have produced the aroma of coffee by heating caffeine, caffetannic acid and sugar.* It would therefore appear that the decomposition products of the proteins and fats are unnecessary and undesirable."

The toxic effect of all these bodies taken together gives coffee its toxicity. Burmann distilled coffee with steam and obtained these volatile constituents, which he examined for the physiological effect. He supposed he had a pure chemical compound, and called it "caffeotoxine." This, however, was proven later by Erdmann to be a mixture of compounds, as before stated.

Burmann's work, which was on treated coffee or that from which the volatile principle had been removed, shows undoubtedly that the injurious effects of coffee are from these compounds by his tests, which he sums up as follows:

(1) From a chemical point of view, treated coffee differs from untreated only in that it contains less of a volatile principle (caffeotoxine).

(2) From a physiological point of view, this constituent alone gives coffee its harmful effects.

(3) The volatile principle has a reducing action on the hæmoglobin; a depressing effect on the blood pressure; a de-

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* This we have been unable to do.

pressing effect on the central nervous system, disturbing the cardiac rhythm; an action on the respiratory centers, causing dypsnea.

(4) The treated coffee contains in normal proportions all the elements of ordinary roasted coffee, with the exception of caffeotoxine, of which it contains only about one-third as much.

(5) The process mentioned (vacuum treatment or steam treatment) is said to eliminate the toxic substances, but not the other elements (fat, caffeine, etc.).

At the 1914 meeting of the American Pharmaceutical Association in Detroit, a paper, read by the author, stated that we had obtained reactions for pyridine in distillates of coffee, but we were unable to make more than an indefinite statement of this, for the reason that, while we had abundant evidence of the presence of pyridine, we had not actually separated it in the pure form.

During the past year in our laboratory we have paid especial attention as to whether pyridine could be separated in small quantities. In the paper referred to, published in the *Journal of the American Pharmaceutical Association* for January, 1915, it was stated that qualitative determinations of the pyridine-like bodies were possible by colorimetric methods, but during the past year we have endeavored to separate pyridine in pure state from finely pulverized roasted coffee. This we have succeeded in doing, even from small quantities of the pulverized roasted bean.

The process used consists in heating a quantity of finely pulverized coffee in a balloon flask contained in an oil bath at about 175° to 200° and connected to a suitable condenser and a vacuum pump by which a pressure of about 4 cm. of mercury was obtained. This distillate, when made strongly alkaline, yielded unmistakably pyridine.

It was thought that, notwithstanding these facts, possibly pyridine might be the result of destructive distillation rather than that this body preëxisted in the roasted coffee bean. In order to prove the latter was the case, namely, that pyridine preëxisted in roasted coffee and presumably was the result of roasting, the following experiment was performed. A few pounds of coffee were macerated for twenty-four hours with dilute hydrochloric acid and then percolated. The resulting percolate was then concentrated and made strongly alkaline and steam distilled. From the distillate we recovered pyridine in the pure form.

In order to ascertain the activity of the concentrate in terms of its physiological action, the concentrate, which was the result of the dry distillation of coffee at a definite temperature and diminished pressure, was collected, hermetically sealed in glass ampules and sent to the laboratories of Parke, Davis & Co., where its toxicity was determined quantitatively by Doctor Hamilton in the biological laboratory of that firm.

Their report is as follows: "The results of our tests indicate that the minimum lethal dose of the concentrate, administered intraperitoneally, for frogs is 0.03 cc. per gram of body weight; for guinea pigs it is about 0.8 cc. per kilo of body weight."

We have just sent to the same biological chemist another lot of concentrate to have additional determinations made, *i. e.*, one to show the effect of internal administration by the mouth of the concentrate.

While coffee contains these toxic principles, it does not necessarily indicate, as some might suppose, that coffee is poisonous. Although some people are so constituted that they cannot use coffee, thousands of others use it without harmful effects, and even seem to receive benefit from its use. Therefore, we should not condemn coffee simply because the toxic principle, which has always existed, has been identified more certainly.

It might be said, in closing, that it is very probable that this toxic principle can be removed. In fact, a process is now in use (vacuum treatment) by which at least part of this principle is expelled, and by further experimentation the process can be further improved. It might be mentioned that this process of removing the volatile principle in the coffee is in exact contradiction to the former theory that it was desirable to retain the volatile principle in the coffee for its supposed aromatic effect.

For valuable collaboration in this work the author is indebted to his associates. Mr. G. N. Watson and Donald H. Lackey.

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